Innovative ways of assessing durable responses to immunotherapy

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Disclosures

• Participation in advisory boards:
MSD, BMS, Merck Serono, GSK, Astra Zeneca, Nanobiotix, Amgen, Roche
Introduction

- Immunotherapy targeting the PD1/PD-L1 axis has been a breakthrough in oncology for several reasons:
  - novelty of the mechanism of action
  - efficacy in multiple tumor types
  - occurrence of durable responses
Melanoma patients treated with ipilimumab

Schadendorf et al., JCO 2015;33:1889-94
NSCLC patients treated with nivolumab

Gettinger et al., JCO 2018;36:1675-84
NSCLC patients treated with nivolumab

Gettinger et al., JCO 2018;36:1675-84
Challenges

• How to define a durable response?
How to define a durable response?

• No definition
How to define a durable response?

• No definition
• Exceptional responders initiative:
  Received a treatment in which fewer than 10% of patients had a CR or a durable PR $> 6$ months

How to define a durable response?

Borcoman et al., Ann Oncol 2019;30:385-396
How to define a durable response?

**HNSCC**

- No. of Patients: Nivolumab 260, Standard Therapy 121
- No. of Events: 150, 103
- Median Progression-free Survival (95% CI): Nivolumab 19–21 months, Standard Therapy 2.3 (1.9–3.1)

- Hazard ratio for disease progression or death: 0.89 (95% CI, 0.70–1.13), P=0.32

**Melanoma**

- Patients Who Died or Had Disease Progression: Nivolumab 108/210, Dacarbazine 163/208
- Median Progression-free Survival (95% CI): Nivolumab 3.5–10.8 months, Dacarbazine 2.2 (2.1–2.4)

- Hazard ratio for death or disease progression: 0.43 (95% CI, 0.34–0.56), P<0.001

Ferris et al., NEJM 2016;375:1856-67; Robert et al., 2015;372:320-30
How to define a durable response?

Durable response = PFS ≥ 3x median PFS of the whole cohort

Pons et al., JCO Precis Oncol 2019
Challenges

• How to define a durable response?
• How frequent are durable responses?
How frequent are durable responses?

• **Meta analysis** of randomized phase III trials that included at least one immunotherapy arm in the R/M setting

• **19** trials

• **11,640** patients

• **42** arms:
  - 26 immunotherapy arms
  - 16 non-immunotherapy arms

Pons *et al.*, JCO Precis Oncol 2019
How frequent are durable responses?

Pons et al., JCO Precis Oncol 2019
Challenges

• How to define a durable response?
• How frequent are durable responses?
• **How to predict a durable response?**
How to predict a durable response?

• **Multivariate analysis:**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coef. [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of ICI:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PD1/PD-L1 agents</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anti-CTLA4 agents</td>
<td>0.73 [0.52 – 0.94]</td>
<td></td>
</tr>
<tr>
<td><strong>Line of therapy:</strong></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>First-line</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Beyond first-line</td>
<td>0.29 [0.05 – 0.52]</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor type:</strong></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-melanoma</td>
<td>-0.02 [-0.26 – 0.22]</td>
<td></td>
</tr>
</tbody>
</table>

Pons *et al.*, JCO Precis Oncol 2019
How to predict a durable response?

CT scan

PET-CT

Tan et al., Ann Oncol 2018;29:2115-20
Challenges

• How to define a durable response?
• How frequent are durable responses?
• How to predict a durable response?
• Should treatment be interrupted?
Should treatment be interrupted?

• Checkmate 153

Key eligibility criteria:
• Advanced/metastatic NSCLC
• ≥1 prior systemic therapy
• ECOG PS 0-2
• Treated CNS metastases allowed

Nivolumab
3 mg/kg IV Q2W
Treatment for 1 year

Continuous nivolumab

Rc

Stop nivolumab

Nivolumab retreatment allowed at PD

Spigel et al., ESMO 2017 (#12970)
Should treatment be interrupted?

Spigel et al., ESMO 2017 (#12970)
Should treatment be interrupted?

• ORR following drug rechallenge:

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Drug</th>
<th>ORR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>25%</td>
<td>Lebbé Ann Oncol 2014</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Ipilimumab</td>
<td>19%</td>
<td>Robert ASCO 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%</td>
<td>Robert CCR 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23%</td>
<td>Chiarion-Sileni BJC 2014</td>
</tr>
<tr>
<td>All</td>
<td>Anti-PD1/PD-L1</td>
<td>25%</td>
<td>Bernard-Tessier EJC 2018</td>
</tr>
</tbody>
</table>

Borcoman et al., Ann Oncol 2019;30:385-396
Should treatment be interrupted?

• Severe toxicity
Should treatment be interrupted?

- Severe toxicity
- Remaining open questions:
  - Should treatment be interrupted after achieving a CR? a PR?
  - How long after achieving a CR (a PR?) treatment should be interrupted?
Challenges

• How to define a durable response?
• How frequent are durable responses?
• How to predict a durable response?
• Should treatment be interrupted?
• How to select patients for single agent immunotherapy?
How to select patients for single agent immunotherapy?

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment
- Known p16 status in the oropharynx

Stratification Factors
- PD-L1 expression (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

Key inclusion and exclusion criteria for KEYNOTE-048 study design:
- Pembrolizumab 200 mg Q3W for up to 35 cycles
- Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk)
- Pembrolizumab 200 mg Q3W for up to 35 cycles total
- Cetuximab 250 mg/m^2 Q1W + Carboplatin AUC 5 OR Cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2/d for 4 days for 6 cycles (each 3 wk)

As assessed using the PD-L1 HC 22C3 pharmDx assay (Agilent), TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. Assessed using the CellSearch p16 Histology assay (Vanadis); cutpoint for positivity = 70%. Following a leading dose of 400 mg/m^2.
How to select patients for single agent immunotherapy?

Progression-Free Survival: P vs E

Overall Survival: P vs E, CPS ≥20 Population

Overall Survival: P vs E, CPS ≥1 Population
How to select patients for single agent immunotherapy?

**Progression-Free Survival: P+C vs E, Total Population**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + Chemo (Pembro + Chemo)</td>
<td>87%</td>
<td>0.92</td>
</tr>
<tr>
<td>EXTREME</td>
<td>91%</td>
<td>(0.77-1.10)</td>
</tr>
</tbody>
</table>

12-mo rate: 16.7%, 12.1%
24-mo rate: 9.8%, 4.6%
Median (95% CI): 4.9 mo (4.7-6.0), 5.1 mo (4.9-6.0)

**Overall Survival: P+C vs E, Total Population**

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<tr>
<th>Events</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + Chemo (Pembro + Chemo)</td>
<td>70%</td>
<td>0.77</td>
</tr>
<tr>
<td>EXTREME</td>
<td>80%</td>
<td>(0.63-0.93)</td>
</tr>
</tbody>
</table>

12-mo rate: 53.9%, 43.9%
24-mo rate: 20.0%, 18.7%
Median (95% CI): 13.0 mo (10.9-14.7), 10.7 mo (9.3-11.7)

Data cutoff date: Jun 13, 2016.
Conclusions

• Defining **durable responders** as patients experiencing a PFS that exceeds **3x the median PFS of the whole population** is a nice way to overcome patients’ **heterogeneity**

• Durable responses are **more frequent** with immunotherapy then with other anticancer agents but are **not specific** to immunotherapy

• Durable responses may be more frequent in **less advanced disease**

• Patients achieving **CR** according to RECIST or **complete metabolic response** on PET CT are more prone to experience a durable response
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